REMARKS

I. Claim Status and Removal of Finality

Claims 16, 22-24, and 29-34 are pending in this application. Applicants note that in the Office Action Summary mailed March 21, 2006, the Examiner indicates that claims 16, 22-24, and 29-32 are pending and stand rejected in the present application. By the Amendment in Response to Non-final Office Action received by the Patent Office on December 20, 2005, Applicants, *inter alia*, introduced new claims 33 and 34. Because the Examiner has not considered claims 33 and 34, Applicants respectfully request removal of the finality of the pending Office Action, entry of the present claim amendments, and consideration of the following remarks in support of the patentability of the pending claims.

II. Amendments to the Claims

By the present amendment, claim 16 has been amended without prejudice or disclaimer to recite "wherein the antibody does not bind to living MCF-7 cells that do not express BCRP on their surface; and does not bind to denatured BCRP." The amendment to claim 16 emphasizes that the claimed antibodies bind to living MCF-7 or 3T3 cells expressing human or murine BCRP on their surface, but do not bind MCF-7 cells that do not express human or murine BCRP on their surface and also do not bind to denatured BCRP. Claims 31 and 33 have been similarly amended to recite that the claimed antibodies "do not bind to denatured BCRP." Support for these claim amendments may be found throughout the specification for example at page 9, lines 22-29, page 23, lines 11-32, page 24, lines 1-8, and page 39, lines 12-24. By these claim amendments no new matter has been introduced. Entry and consideration of these claim amendments is respectfully requested.

III. Formalities

The Examiner contends that the information disclosure statement filed with the response of December 20, 2005, lacked a complete statement as specified in 37 C.F.R. 1.97(e). Applicants submitted a complete information disclosure statement as evidenced by the attached copy of the

Certificate of Express Mailing listing the information disclosure statement and IDS citation filed by Applicants on December 20, 2005. To complete the record, a duplicate copy of the information disclosure statement, PTO/SB/08, and check number 10668 are submitted herewith.

Furthermore, Applicants respectfully disagree with the Examiner's assertion that "[t]he information disclosure statement filed 12/20/2005 fails to comply with 37 C.F.R. 1.97(c) because it lacks a complete statement as specified in 37 C.F.R. 1.97(e)." On the contrary, 37 C.F.R. 1.97(c) recites as follows:

> (c) An information disclosure statement shall be considered by the Office if filed after the period specified in paragraph (b) of this section, provided that the information disclosure statement is filed before the mailing date of any of a final action under § 1.113 ... and it is accompanied by one of:
>
> (1) The statement specified in paragraph (e) of this section; or
>
> (2) The fee set forth in § 1.17(p). [Underscore Added].

Because Applicants' Information Disclosure Statement filed on December 20, 2005 was filed during the pendency of the Non-final Office Action mailed July 28, 2005, Applicants' Information Disclosure Statement was filed before the mailing date of a final action under § 1.113. And, because Applicants' Information Disclosure Statement filed on December 20, 2005 included check number 10668 in the amount of $405.00 as payment for a two (2) month extension of time ($225.00) and the fee for submitting the Information Disclosure Statement ($180.00), Applicants' Information Disclosure Statement was accompanied by "[t]he fee set forth in § 1.17(p)". Thus, Applicants respectfully submit that they did comply with the requirements of 37 C.F.R. 1.97(c) and that a "statement specified in paragraph (e) of this section" is not required.

Applicants' request withdrawal of the present objection and consideration of the references submitted by the Information Disclosure Statement filed 12/20/2005.

IV. Withdrawn Rejections under 35 U.S.C. §112, first paragraph

The Examiner is thanked for notifying Applicants that the previous written description and enablement rejections under 35 U.S.C. § 112, first paragraph are now withdrawn in view of the recent decisions in *Noelle v. Lederman*, 355 F.3d 1334 (Fed. Cir. 2004) and *SmithKline Beecham Corporation v. Apotex Corp.*, 403 F.3d 1328 (Fed. Cir. 2005).

V. Claim Objections

Claims 16, 22-24, and 29-32 stand objected to for allegedly failing to further limit the claimed subject matter. The Examiner alleges that the phrase 'wherein the antibody fails to bind to living MCF-7 cells that do not express BCRP' does not appear to further describe a functional characteristic of the antibody. However, this phrase emphasizes an important feature of the claimed antibodies. Claims 16, 31, and 33 have been amended to further emphasize the conformation-specific recognition aspect of the present antibodies, as described above in Section II. The phrase further describes the inventive antibodies by excluding antibodies that cross-react with living MCF-7 cells that do not express human or murine BCRP. As described in the specification at page 24, lines 1-9 and in Figure 1, it is possible for observed reactivity to be due not to anti-huBCRP activity, but to a murine antibody that cross-reacts with a surface protein found on the MCF-7 cell. Thus, the phrase further characterizes and distinguishes the claimed antibodies and is proper.

Claims 16, 31, and 33 have also been amended to include the phrase "the antibody does not bind to denatured BCRP." This phrase excludes antibodies that also bind to denatured BCRP. It is possible to have BCRP antibodies that bind to an epitope from an extracellular BCRP region and also to an epitope present in denatured BCRP. The added phrase distinguishes between conformational specific BCRP antibodies that also bind to denatured BCRP and conformational antibodies that do not bind to denatured BCRP. For these reasons, Applicants submit that the new claim phrases describe physical properties of the claimed antibodies and request that the objections to claims 16, 22-24, and 29-32 be withdrawn.

VI. Rejections under 35 U.S.C. §103

Claims 16, 22-24, and 29-32 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Ross *et al.* U.S. Patent No. 6,313,277 ("Ross") in view of Mechetner *et al.* U.S. Patent No. 5,994,088 ("Mechetner"). The Examiner alleges that "amended claim 16 adds a phrase describing the binding specificity of the claimed antibody, which is the intrinsic property of the antibody produced by the combined teachings of the cited references" (Office Action at page 4) and that the claimed antibodies could reasonably be produced by the teachings of Ross relating to the general knowledge of the BCRP antigen in combination with the methods described in Mechetner.

Applicants respectfully traverse the stated grounds for rejection of claims 16, 22-24, and 29-32 and submit that the cited references, viewed for the whole of their teachings, neither teach nor suggest the presently claimed invention.

Applicants' instant claims, as presently amended, are directed, *inter alia*, to isolated antibodies that bind to an extracellular portion of a human or murine Breast Cancer Resistance Protein (BCRP) wherein the extracellular portion of the BCRP is in its natural conformation and wherein the antibody binds to living MCF-7 or 3T3 cells expressing BCRP on their surface. Antibodies according to the presently claimed invention do not bind to living MCF-7 cells that do not express BCRP on their surface and do not bind to denatured BCRP.

Ross is directed generally to a breast cancer resistance protein (BCRP) and to cDNAs encoding BCRP. A stated object of Ross is to provide antibodies directed against BCRP for use as BCRP antagonists. In this regard, Ross states that polyclonal antibodies to BCRP "can be prepared by immunizing a mammal with a preparation of BCRP or functional derivative of BCRP." Ross does not, however, teach the actual generation of any antibody whatsoever and neither teaches nor suggests the generation of antibodies that bind to BCRP in its natural conformation on the surface of a living cell and that do not bind to denatured BCRP. Thus, Ross neither teaches nor suggests the presently claimed invention.

Mechetner does not remedy the deficiencies noted in the Ross reference because Mechetner neither teaches nor suggests antibodies to BCRP. On the contrary, Mechetner is directed generally to methods and reagents for preparing immunological agents, including antibodies,

directed to P-Glycoprotein (Pgp). As described in further detail below, Pgp is quite distinct both structurally and functionally from BCRP and there is nothing about the teachings of Mechetner that would lead one of ordinary skill in the art to achieve Applicants' presently claimed antibodies that bind to BCRP in its natural conformation and that do not bind to denatured BCRP. Thus, there is nothing in the teachings of Mechetner that remedy the deficiencies in Ross and/or that would have motivated the ordinarily skilled artisan to achieve, with a reasonable expectation of success, Applicants' claimed antibodies.

Applicants respectfully disagree with the Examiner's position that one skilled in the art could have achieved antibodies that bind to BCRP on living cells and in its natural conformation that do not otherwise bind to denatured protein by relying on the BCRP antigen taught by Ross in view of the methods for antibody production and screening taught by Mechetner. On the contrary, Mechetner expressly teaches the use of mouse cells, *i.e.* BALB/c/3T3 1000 cells (column 12, lines 38-45) to generate and screen for antibodies specific for Pgp to find a single monoclonal antibody (UIC2) out of a total of 556 clones.

The detailed methods for obtaining UIC2 are further described by reference to Mechetner and Roninson, "Efficient Inhibition of P-glycoprotein-mediated multidrug resistance with a monoclonal antibody," *Proc. Natl. Acad. Sci. USA*, 89:5824-5828 (1992) (a copy is submitted herewith for the Examiner's convenience). For example, at page 5825, column 1, second full paragraph, Mechetner states that:

> Hybridoma supernatants were screened by indirect immunofluorescence microscopy of live BALB/c 3T3 and BALB/c 3T3-1000 cells. One hybridoma clone of 556 clones tested produced a mAb, termed UIC2, which was reactive with BALB/c 3T3-1000 but not with parental BALB/c 3T3 cells. [Underscore added].

In contrast, the present invention was achieved with a unique immunization and screening methodology, which methodology employed a human cell line as described at page 39, lines 14-24:

> The 3T3-BCRP cells were used to immunize mice. Twenty BALB-C mice were immunized with whole, living 3T3-BCRP cells by injecting 4 million

> cells directly into the peritoneal space. Fourteen days later, these cells were reinjected as an immunization boost. Individual mice that showed antibody reactivity in the serum were killed and hybridoma clones were isolated after cell fusion and selection with HAT media. Supernatants from each hybridoma clone were screened by flow cytometry using a human breast cancer cell line (MCF-7) that had been transduced with an amphotrophic HaBCRP vector. Any supernatant that showed reactivity in this assay was then back-screened on the parental MCF-7 lines, and clones that reacted with the MCF-7 HuBCRP cells but not with the parental MCF-7 line were scored as positive and specific. These cells were then subcloned, and re-screened on the indicator cell lines (see Figure 1). [Underscore added].

Using a murine cell line for immunization and a human cell line for screening enabled Applicants to overcome the deficiencies in the art, such as the non-specific background and low efficiency inherent in the methods used by Mechetner. The advantages of this back-screening method are illustrated in Figure 1 and are also discussed on page 23, lines 11-32, through page 24, lines 1-8 where Applicants describe eliminating clones that react with the parental (non-transduced) MCF-7 cells. Absent these teachings, the ordinarily skilled artisan would not have envisioned success in achieving any antibodies directed against a natural protein in a living cell much less an antibody that binds to natural BCRP in living cells but not to denatured BCRP. There's simply nothing in the teachings of Mechetner that would have motivated a skilled artisan to attempt the generation and isolation of antibodies having the instantly claimed binding properties or that would have provided the artisan with a reasonable expectation of success in achieving such antibodies. In this regard, Mechetner's method for producing UIC2 did not employ, or even contemplate, the use of murine cells for immunization and human cells for screening. On the contrary, Mechetner specifically teaches the use of murine cells for both steps of immunization and screening and provides no suggestion for using a cell type for the screening step that is different than that used in the immunization step. Applied to the present invention, the use of murine cells for immunization and screening would have resulted in the generation of a high level of background, non-specific antibodies having no binding specificity for natural BCRP on living cells. Since the teachings of Mechetner would not have led one of ordinary skill in the art to the use of murine cells for immunization and human cells for screening, an ordinarily skilled artisan would not have had a

reasonable expectation of success in achieving the presently claimed antibodies against natural BCRP in living cells.

Furthermore, Mechetner is silent with respect to the distinction between antibodies that bind to denatured Pgp protein versus antibodies that do not bind to denatured Pgp protein. Absent such a teaching, it cannot be said that the teachings of Mechetner in any way contemplate antibodies having functional characteristics that parallel the anti-BCRP antibodies of the present invention. Thus, the combination of Ross in view of Mechetner neither teaches nor suggests a method for achieving Applicants' claimed antibodies that bind to natural BCRP on living cells but not to denatured BCRP.

As pointed out in the December 20, 2005 Amendment filed in response to the July 28, 2005 Office Action, Mechetner describes antibodies to the Pgp protein, which protein exists as a monomeric transporter. The structure of Pgp is in stark contrast to the structure of human BCRP, which, as Applicants describe in the specification at page 41, lines 9-17, shares the highest primary structural homology with the Drosophila white gene product -- a "half transporter" that requires homo or heterodimerization in order to achieve an active conformation and consequent functionality, such as ATP hydrolysis. Thus, Applicants respectfully submit that there is nothing in the teachings of Mechetner for achieving a single antibody directed to a monomeric transporter that would have motivated one of ordinary skill in the art to attempt to raise antibodies against the BCRP protein of Ross to achieve antibodies that bind to a natural BCRP protein in a living cell as provided by the instant claims.

In fact, Applicants note that prior to the instant application no one had successfully achieved the production of antibodies that specifically bind to a human or murine BCRP expressed on a living cell. As late as 2004, experiments described in journal articles authored by Ross still utilized the BXP-34 antibody, described by Scheffer *et al.*, *Cancer Res.* 60:2589-2593 (2000) (previously submitted) as being "unable to stain viable unfixed BCRP-positive cells, which showed that the mAb detected an internal epitope of the BCRP protein." (See pp 2591-2592). Thus, prior to Applicants' disclosure of antibodies that bind to natural BCRP on living cells, those of ordinary

skill in the art, including Ross and co-workers, did not have access to or an understanding of how to achieve conformational monoclonal antibodies such as, for example, Applicants' 5D3, 7A3, 1C5 and 8C2 monoclonal antibodies, each of which exhibit binding specificity for BCRP expressed on the surface of living cells while being incapable of binding to denatured BCRP.

Furthermore, Applicants respectfully disagree with the Examiner's suggestion that there is anything contradictory in the previously filed Declarations of Sarkadi and/or Sorrentino. On the contrary, the Sarkadi Declaration addresses the state of the art prior to Applicants' disclosure and the Sorrentino Declaration addresses Applicants' disclosure, for the first time, of methodology for achieving conformational monoclonal antibodies exhibiting binding specificity for BCRP expressed on the surface of living cells but being incapable of binding to denatured BCRP. Applicant's achievement is underscored by deficiencies in the teachings of Ross, which deficiencies are not remedied in any way by the teachings of Mechetner, wherein Ross describes the use of the antibody BXP-34 (at least through the year 2004), which antibody is, based on the express disclosure of Scheffer *et al.*, incapable of binding to a natural BCRP protein expressed on the surface of a living, *i.e.*, "viable unfixed BCRP-positive cell[ ]." Thus, clearly, there is nothing in the disclosure of Ross or Mechetner that supports the Examiner's position that antibodies made by the methodology of Mechetner against the BCRP protein disclosed in Ross would "intrinsically" bind to natural BCRP on living cells but not to denatured BCRP as expressly recited in the instant claims.

Nothing in the references cited by the Examiner, viewed as a whole, either teach or suggest Applicants presently claimed invention. Nothing in the cited references teaches or suggests the optimized immunization and screening methodology for obtaining the inventive antibodies as described in the specification (at, for example, Figure 1; at page 23, lines 11-16; and at page 39, lines 14-24). And, nothing in the cited references hints at any expectation of success of utilizing the teachings of Ross and Mechetner to obtain conformation specific BCRP antibodies that fail to bind denatured BCRP. On the contrary, the repeated use by Ross and co-workers of antibodies BXP-34 and BXP-21 as recently as 2004 underscores the failure of others to achieve BCRP antibodies specific for the extracellular portion of BCRP in its natural conformation. Nothing in the cited

references teaches distinguishing between conformational specific BCRP antibodies that also bind to denatured BCRP and conformational antibodies that fail to bind to denatured BCRP.

Because the combined teachings of Ross in view of Mechetner fail to either teach or suggest the claimed antibodies, and since one of ordinary skill in the art would have had no reasonable expectation of success in making Applicants' claimed antibodies guided by the combined teachings of these references, Applicants' invention cannot be obvious in view of the cited art. Applicants believe the presently amended claims are in condition for allowance and respectfully request that the Examiner issue a Notice to that effect.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of this application. In light of the foregoing amendments and remarks, the specification and pending claims are in condition for allowance. Allowance of the application is earnestly solicited.

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Respectfully submitted,

By _____

Gary M. Myles, Ph.D.
Registration No.: 46,209
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(206) 262-8927
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant